

# Considering General Use of MCV4 Among Children Aged 2-10 Years

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# Meningococcal Disease Prevention, United States

- An evolving strategy
  - A single conjugate vaccine (MCV4) available for use in 2-55 year-olds
  - Covering serogroups A,C,Y, W-135
  - Several vaccines in the pipeline targeting infants, toddlers, and adolescents
  - Vaccines including serogroup B
- Long-term goal to prevent all cases of meningococcal disease

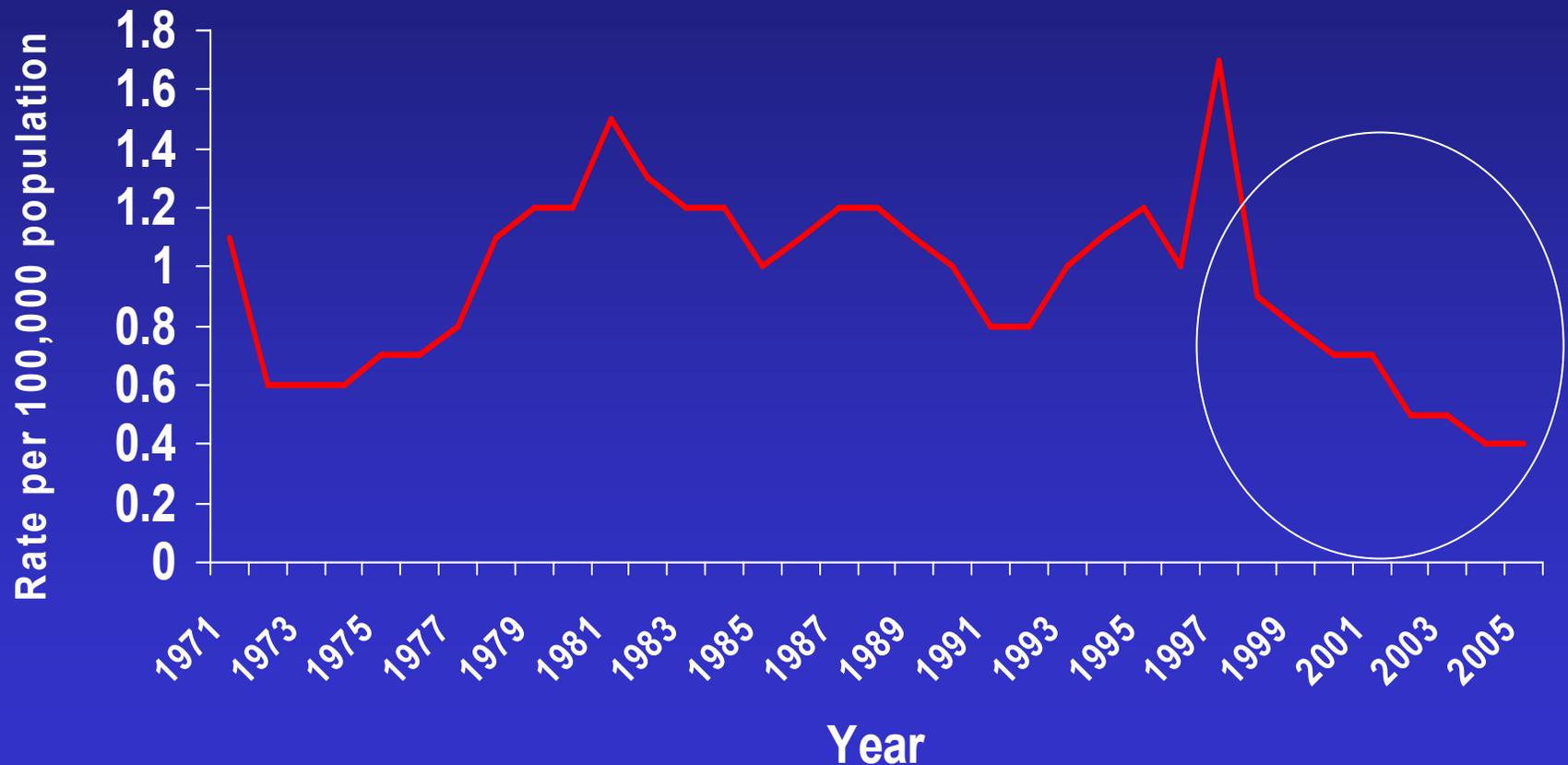
## But for now....

- Adolescents aged 11-18 years recommended for routine MCV4 vaccination
- AND high-risk people aged 2-54 years
- Should ACIP recommend routine MCV4 vaccination in 2-10 year olds?

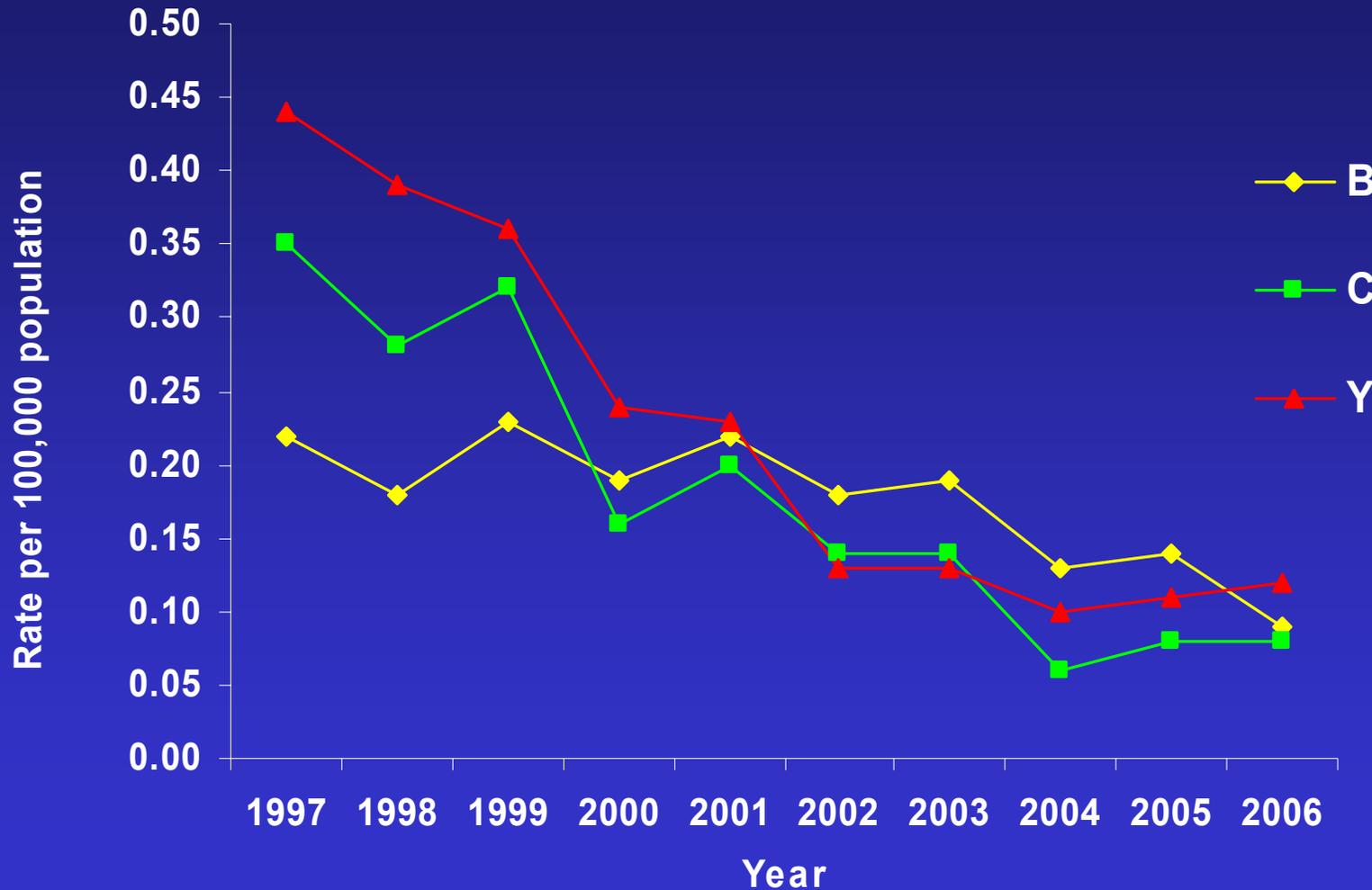
# Working Group Considerations

- Burden of Disease
- Population Impact
- Economic Analysis
- Vaccine Safety
- Vaccine- Immune Response
- Programmatic Implications

# Meningococcal Disease Incidence and Case-Fatality, United States 1970-2005

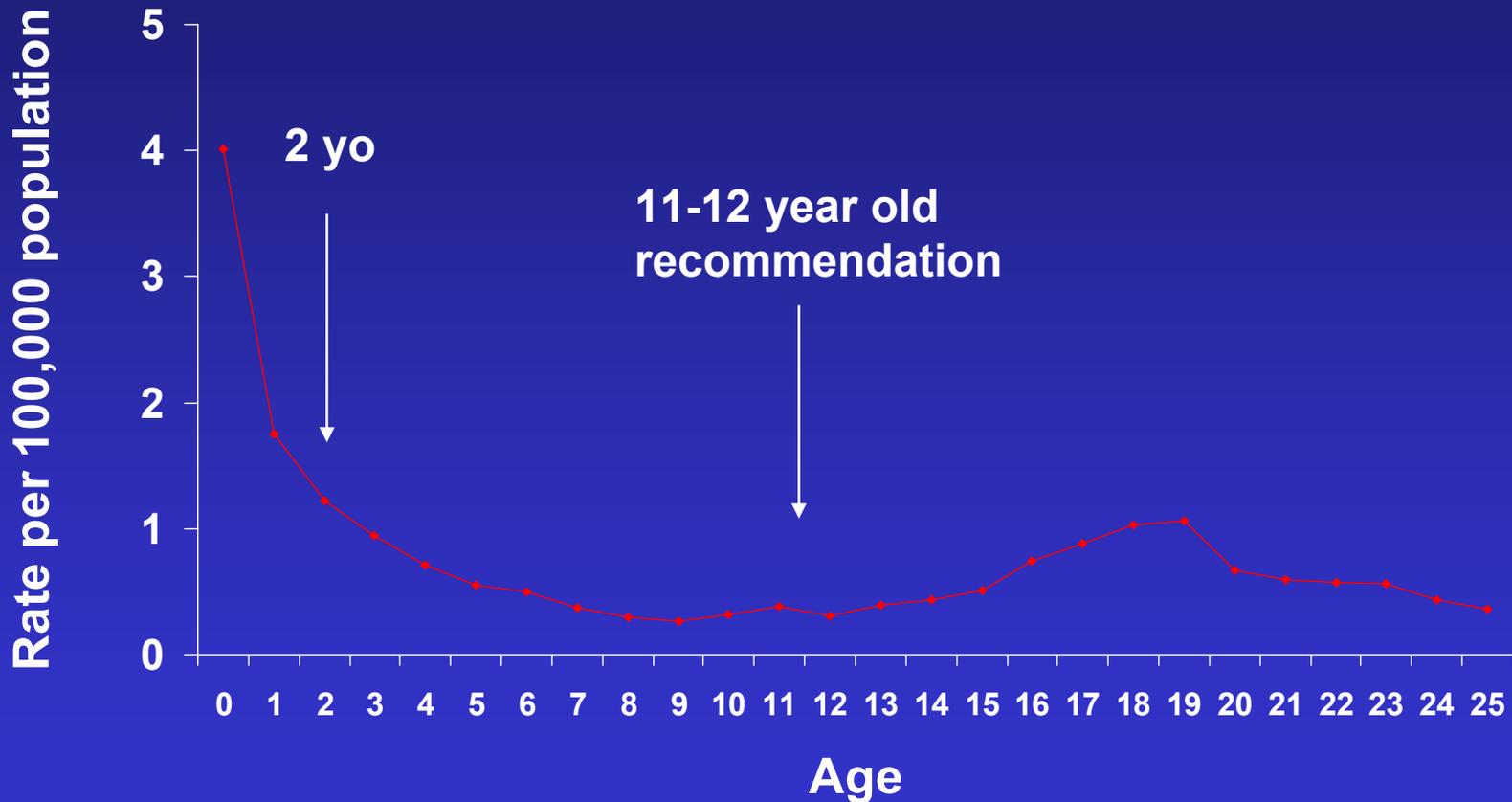


# Projected Rates of Meningococcal Disease by Year, 1997-2006



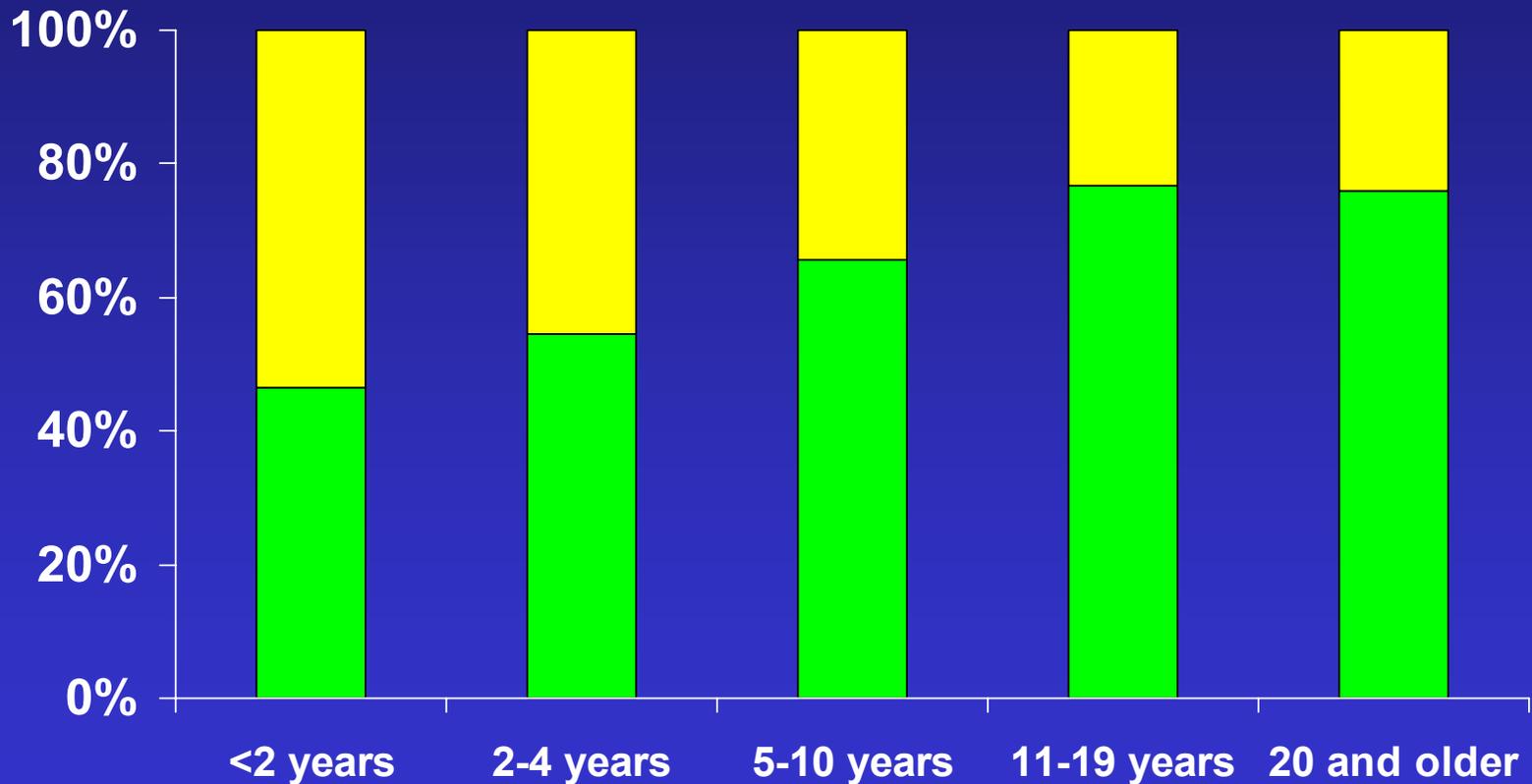
ABCs cases from 1997-2006 and projected to the U.S. population

# Rate of Meningococcal Disease by Single Age Year - All Serogroups

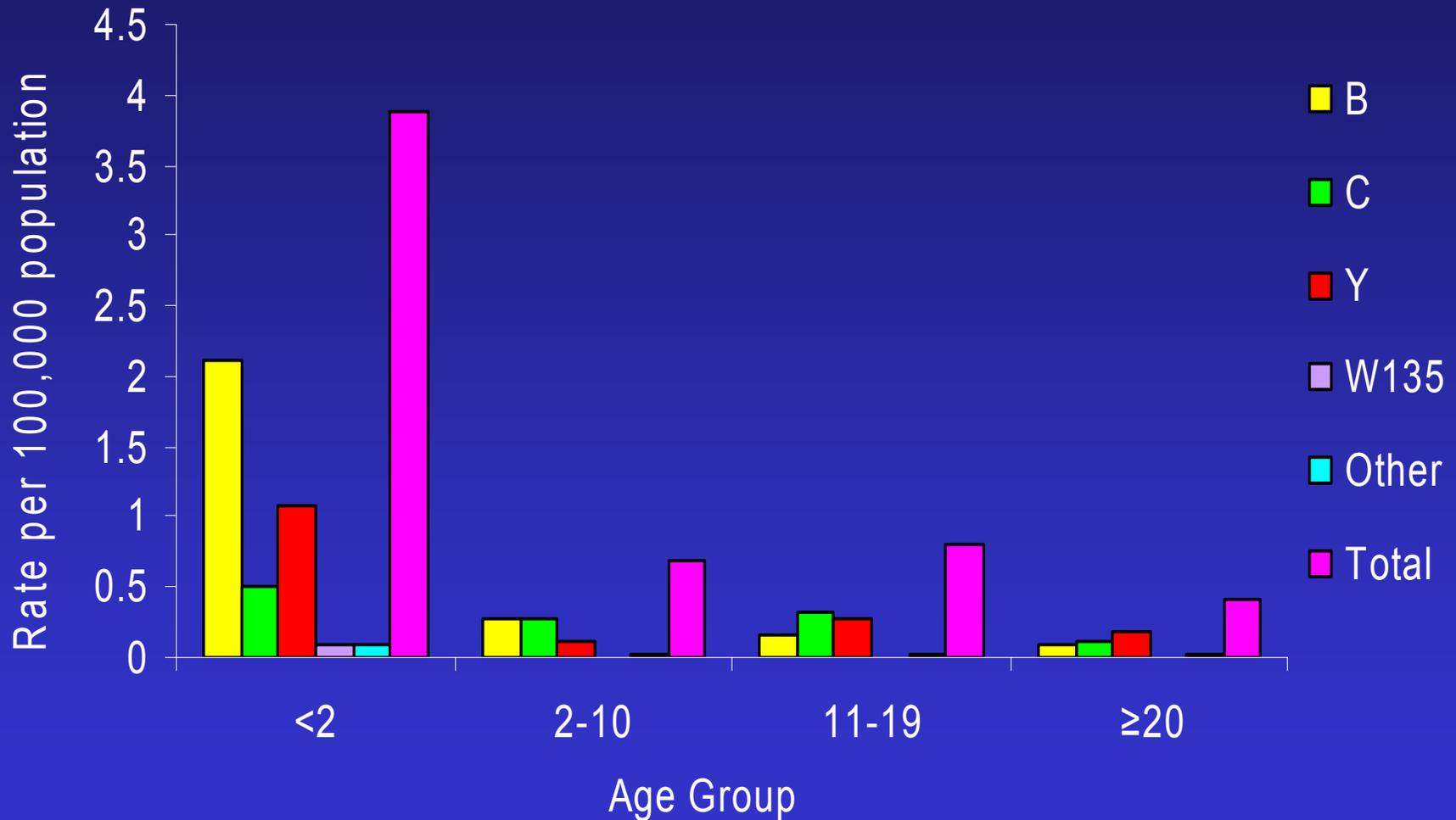


# Proportion of Serogroup A,C,Y,W-135 Meningococcal Disease, 1996-2005

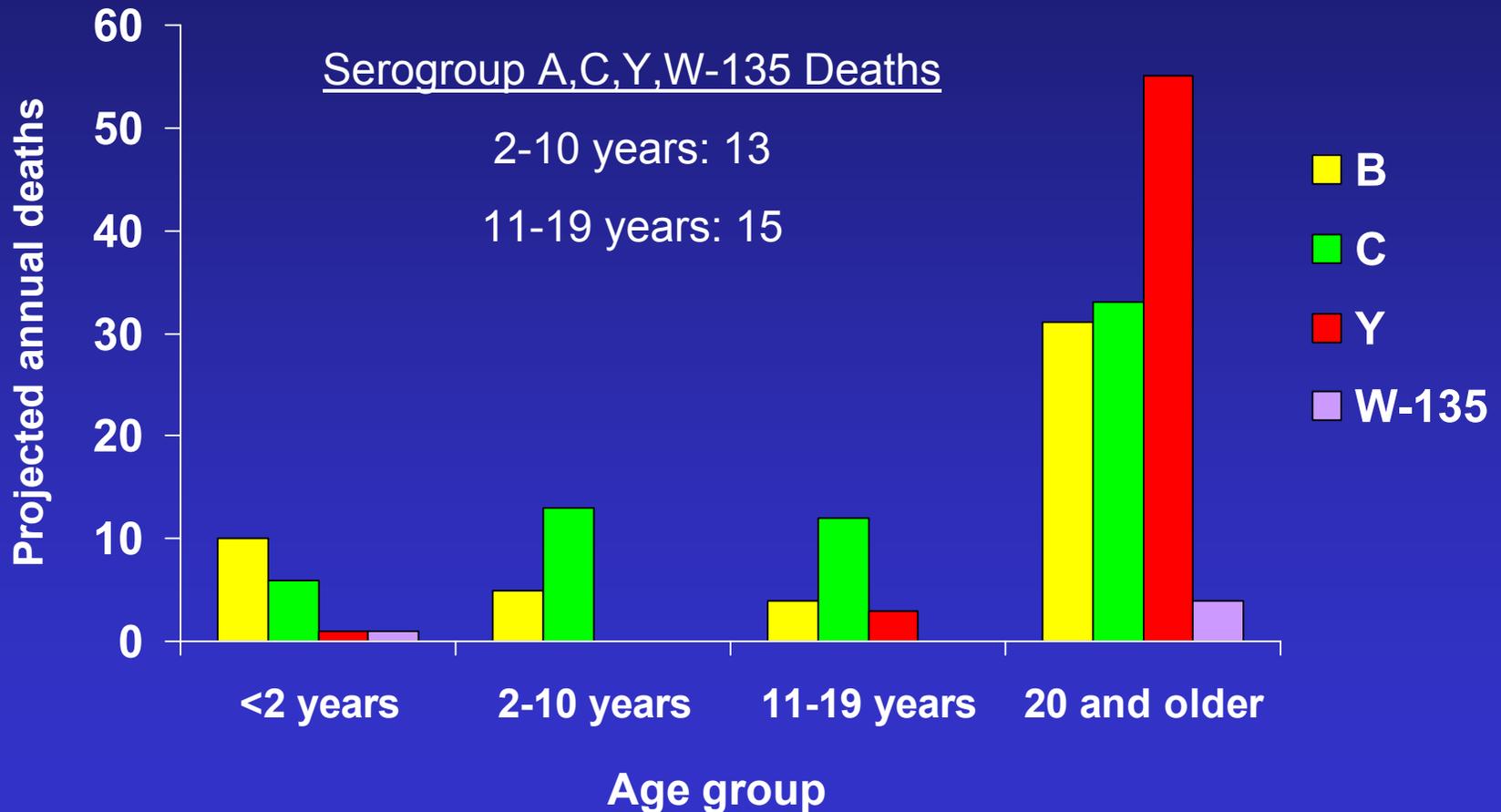
■ Serogroups A, C, Y, W-135 ■ Serogroups B, NG, Other



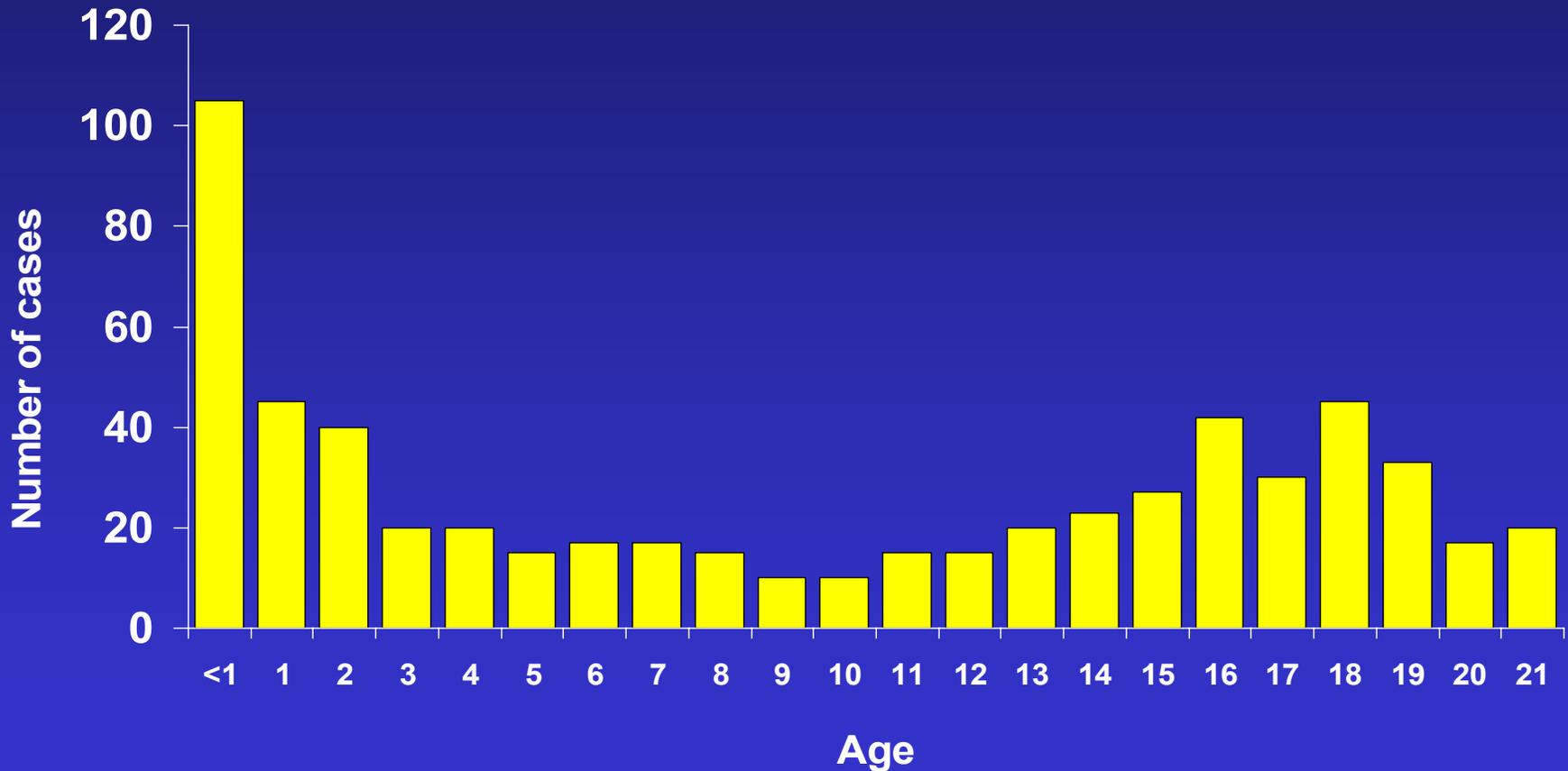
# Rates of Meningococcal Disease by Serogroup, 1997-2006



# Estimated Number of Deaths Annually from Meningococcal Disease, 1997-2006



# Estimated Annual Number of Cases of Serogroup A,C,Y,W-135 Meningococcal Disease, United States: Age 0 - 21 years



# Estimated Annual Cases of A,C,Y,W-135 Meningococcal Disease

- Age 2-10 years: 160 cases
  - 2 years= 40 cases (25%)
  - 2-4 years= 80 cases (50%)
  
- Age 11-19 years: 250 cases

# Working Group Considerations

Routine Vaccination

2-10 year-olds

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Burden of Disease

+/-

Population Impact

Economic Analysis

Vaccine Safety

Vaccine- Immune Response

Programmatic Implications

# Population Impact

- In most studies, young children have low prevalence of carriage of *Neisseria meningitidis*
- Adolescents are generally considered a reservoir of carriage

# Nasopharyngeal carriage, by age

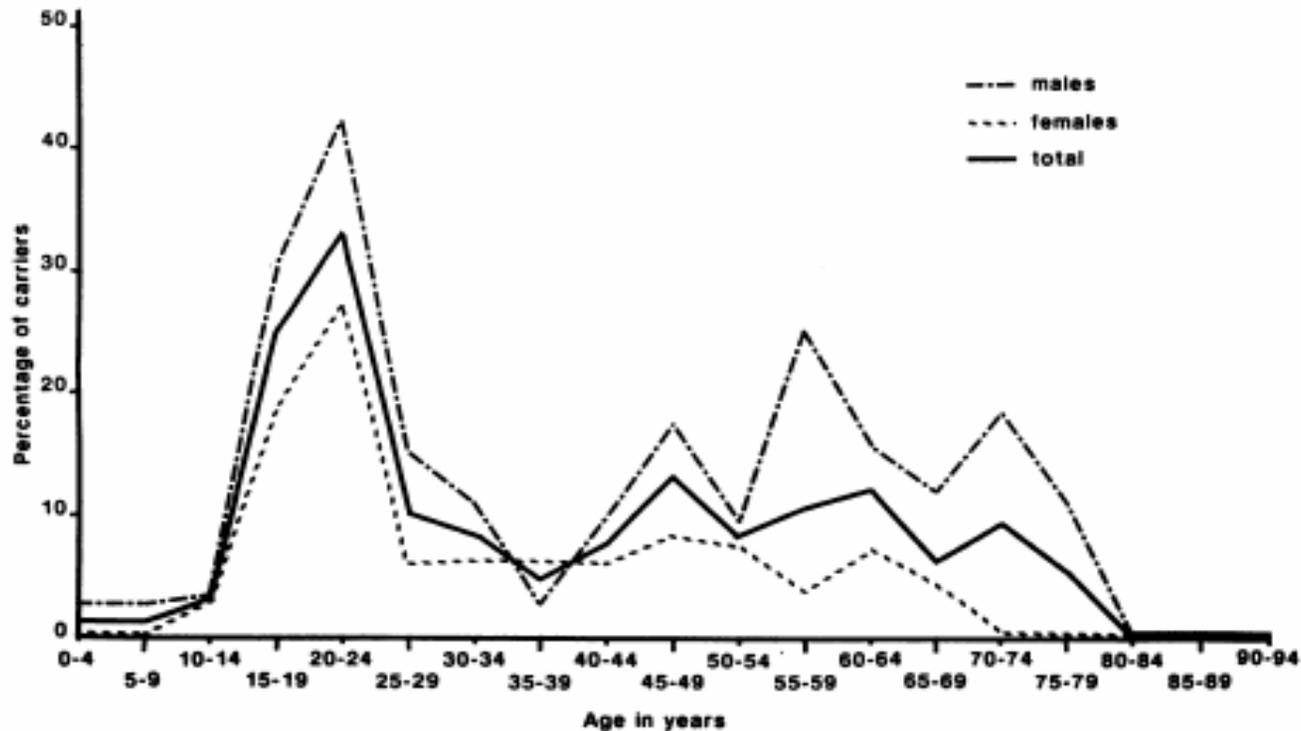


FIG. 1. Percentages of carriers of *N. meningitidis* according to age among males, females, and all participants in a random sample of the Norwegian population.

# Working Group Considerations

Routine Vaccination

2-10 year-olds

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+/-

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-

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# Cost-effectiveness of Vaccinating Young Children with MCV4\*: Model Design

- Monte Carlo simulation analysis
- Hypothetical population
  - 4 million birth cohort
  - 4 million adolescent cohort (11 yos)
- Time Frame: 22 years
- Analytic Horizon: Age-specific Life Expectancy
- Discount rate: 3% (0%-5%)

# Epidemiologic Data

- Age- year- and C+Y+W135 serogroup-specific incidence rates using ABCs data (1991-2005)
- Age- and serogroup-specific case fatality ratios
- Proportion of survivors with sequelae by condition
- Vaccine efficacy per strategy
- Duration of vaccine efficacy: 10 years
- Coverage assumptions
  - Toddlers at 24 mos- 91%
  - Adolescents at 11 yrs- 70%

# Results: No vaccination

per 4M Cohort: Median (5<sup>th</sup>, 95<sup>th</sup> Percentile)\*

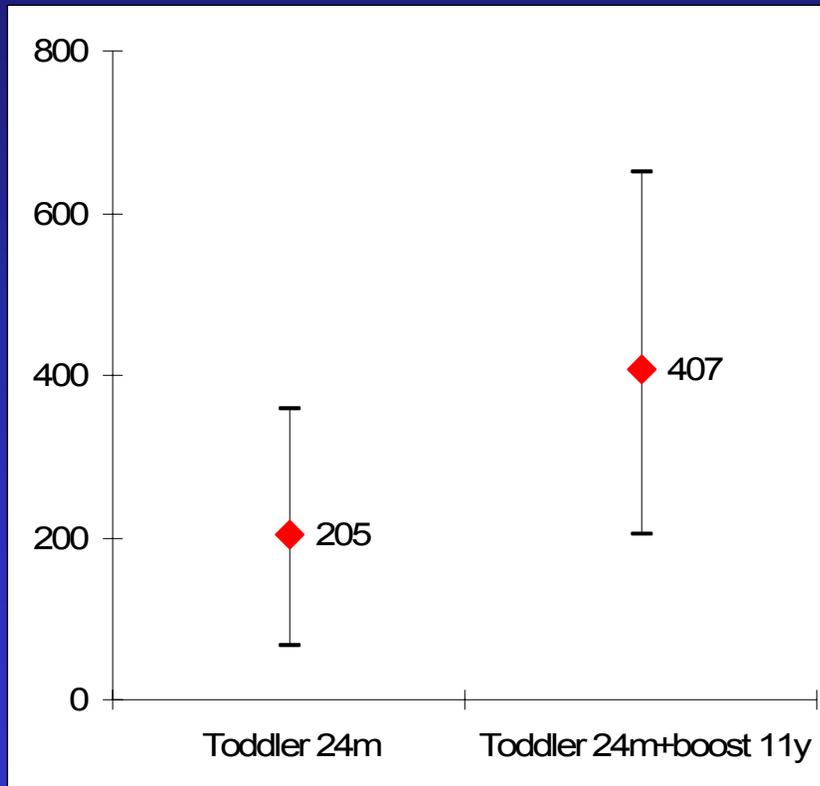
	<b>Adolescent Cohort</b> 11 to 32 yrs	<b>Birth Cohort</b> 0 to 22 yrs
Cases	468 (225-754)	788 (483-1,123)
Deaths	29 (11-52)	43 (21-76)
Life years lost	2,074 (966-3,661)	2,575 (1,446-3,990)
QALY's lost	4,796 (1,500- 11,828)	6,625 (2,902-13,073)
Total cost of illness (in Millions \$)	\$112 (\$52-\$194)	\$144 (84-223)

\* Estimates from Monte Carlo Simulation

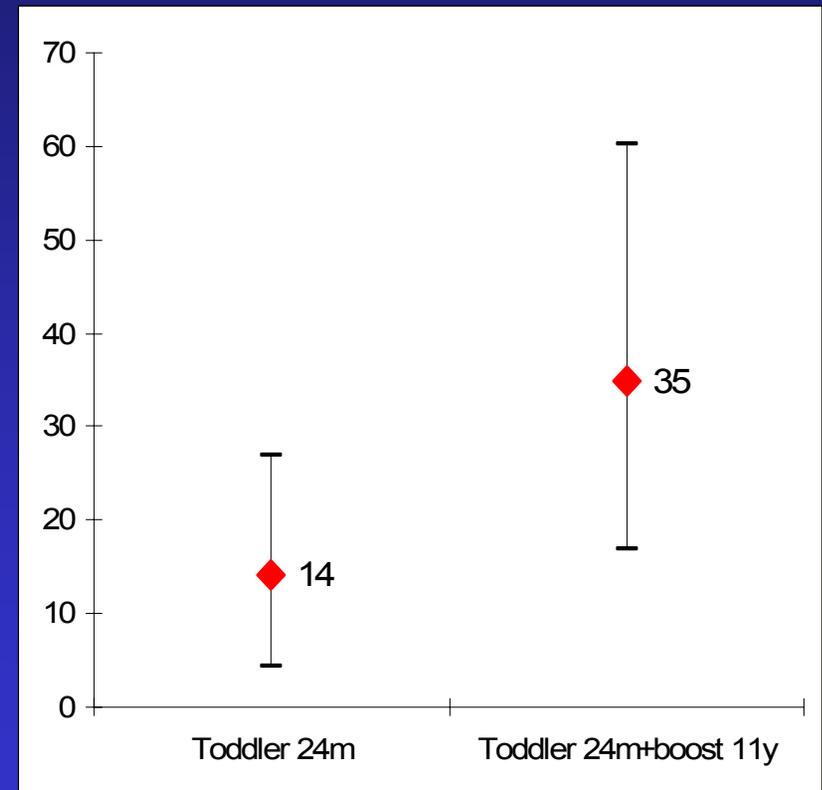
# Cases & Deaths Prevented per 4M Birth Cohort

Median, 5<sup>th</sup> and 95<sup>th</sup> Percentiles\*

## CASES



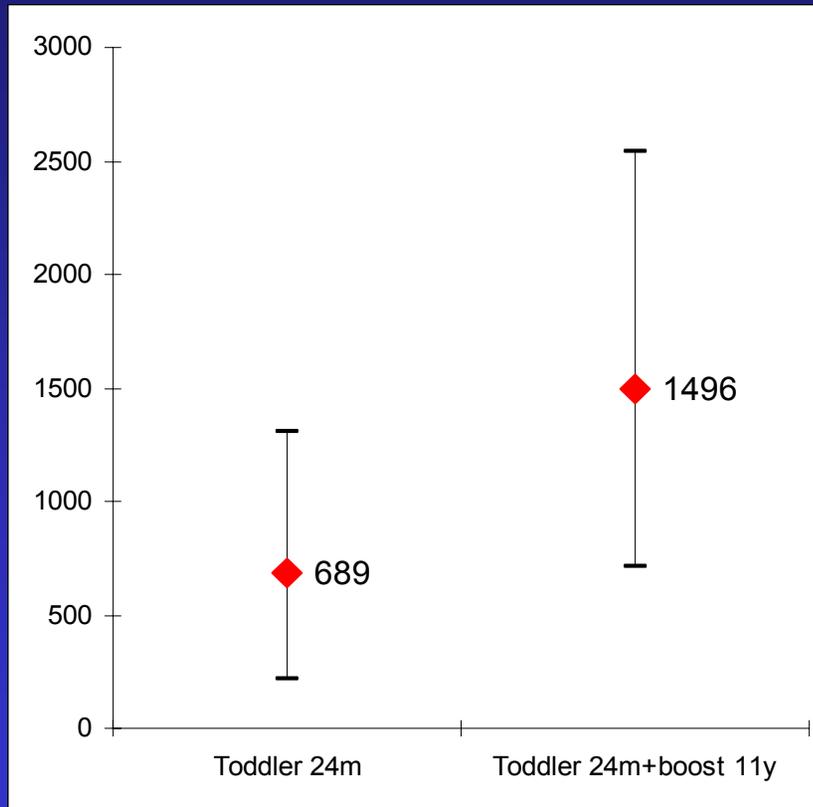
## DEATHS



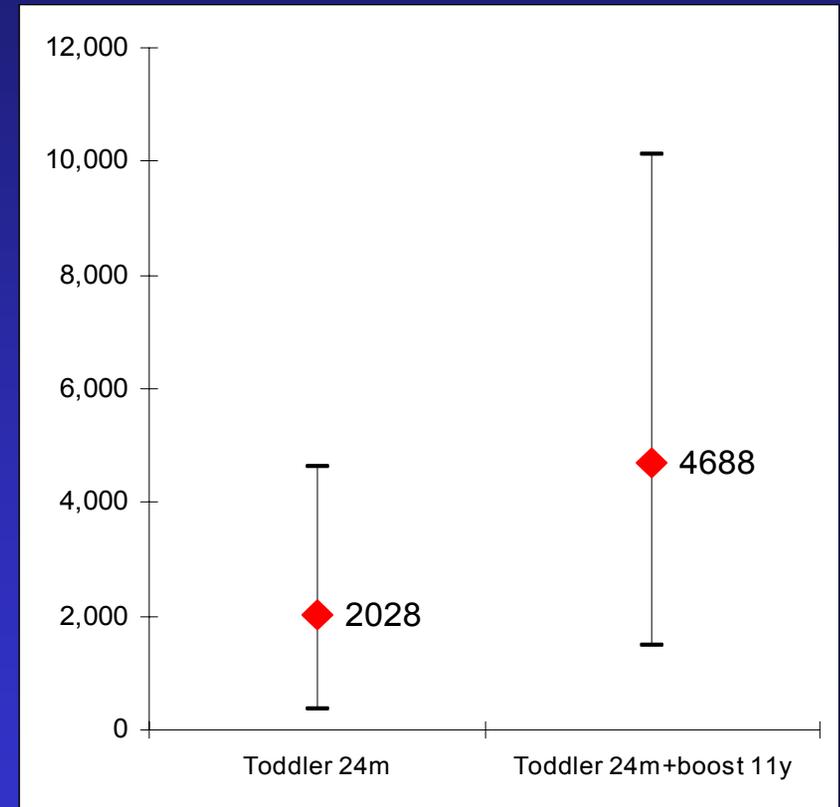
\* Estimates from Monte Carlo Simulation

# Life-years & QALYs saved\* per 4M Birth Cohort Median, 5<sup>th</sup> and 95<sup>th</sup> Percentiles\*\*

## Life-years saved



## QALYs saved

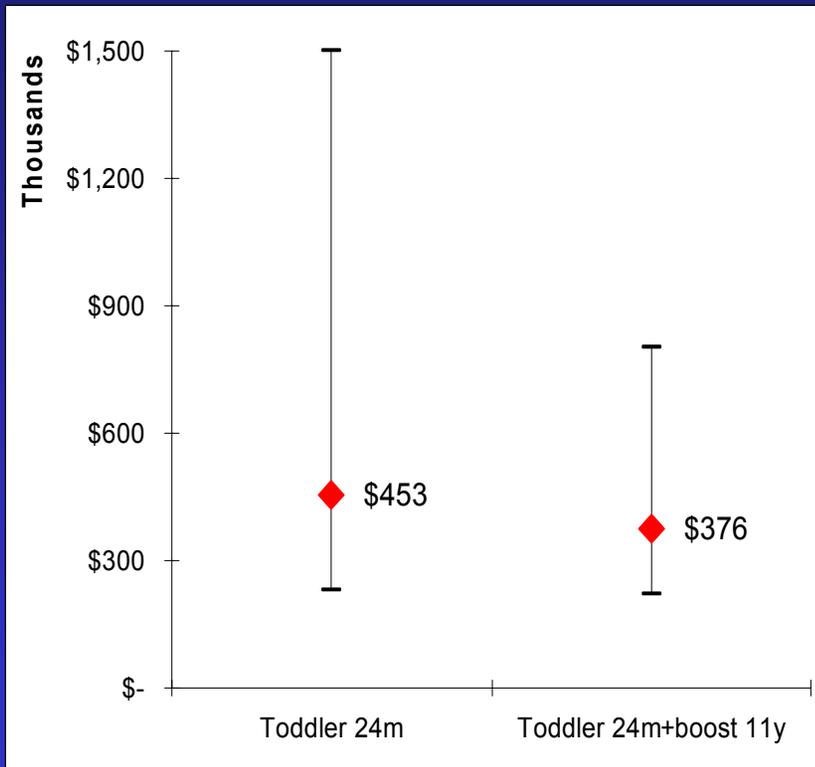


\* Undiscounted

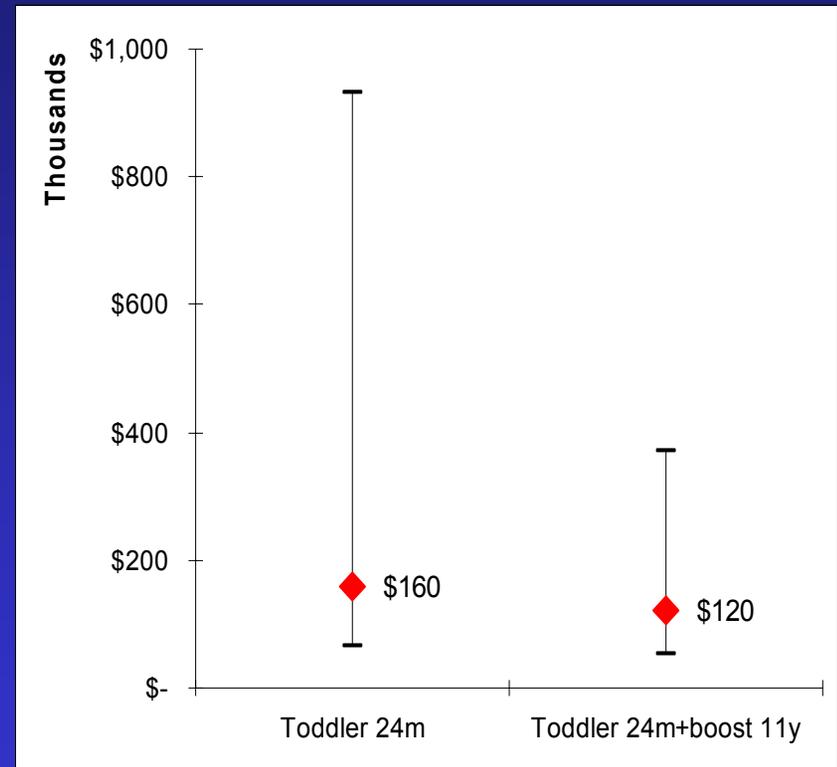
\*\* Estimates from Monte Carlo Simulation

# Cost per LYS & QALY saved\* per 4M Cohort Median, 5<sup>th</sup> and 95<sup>th</sup> Percentiles\*\*

## \$/Life-year saved



## \$/QALY saved



\* Cost per dose \$93 (\$50-\$130) including adm+AE+wastage

\*\* Discounted 3% and excluding indirect cost from deaths

# Comparisons

Intervention	Doses/ vaccine	Cost per vaccinee	Societal \$/LYS	Societal \$/QALY
Toddler 24mos	1-MCV4	\$95	\$453,000	\$160,000
Toddler 24mos+ boost 11y	2-MCV4	\$156	\$376,000	\$120,000
Adolescents 11 yos	1 -MCV4	\$95	\$261,000	\$90,000
Toddler 12 mos *	1-MCV4	\$83	\$166,000	\$105,000
Infants 2-4-6 mos*	3-MCV4	\$232	\$482,000	\$271,000
1 <sup>st</sup> -year college students in dorms **	1 -	\$70	\$297,000	n/a
Meningitis prevented in infants with PCV7***	4-	\$232	\$316,000	n/a

\* Shepard et al., *Pediatrics* 2005 (20 yrs duration of efficacy, data 1993-2002)

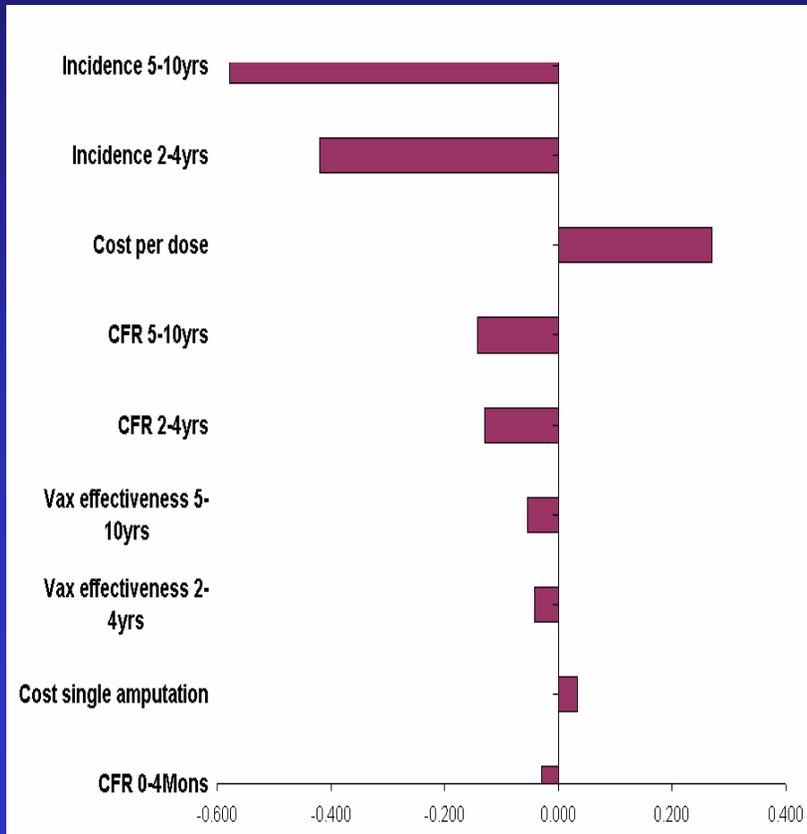
\*\* Scott et al., *Am J Prev Med* 2002 (with updated values)

\*\*\* Lieu et al *JAMA* 2000 (with updated values)

# Sensitivity Analyses

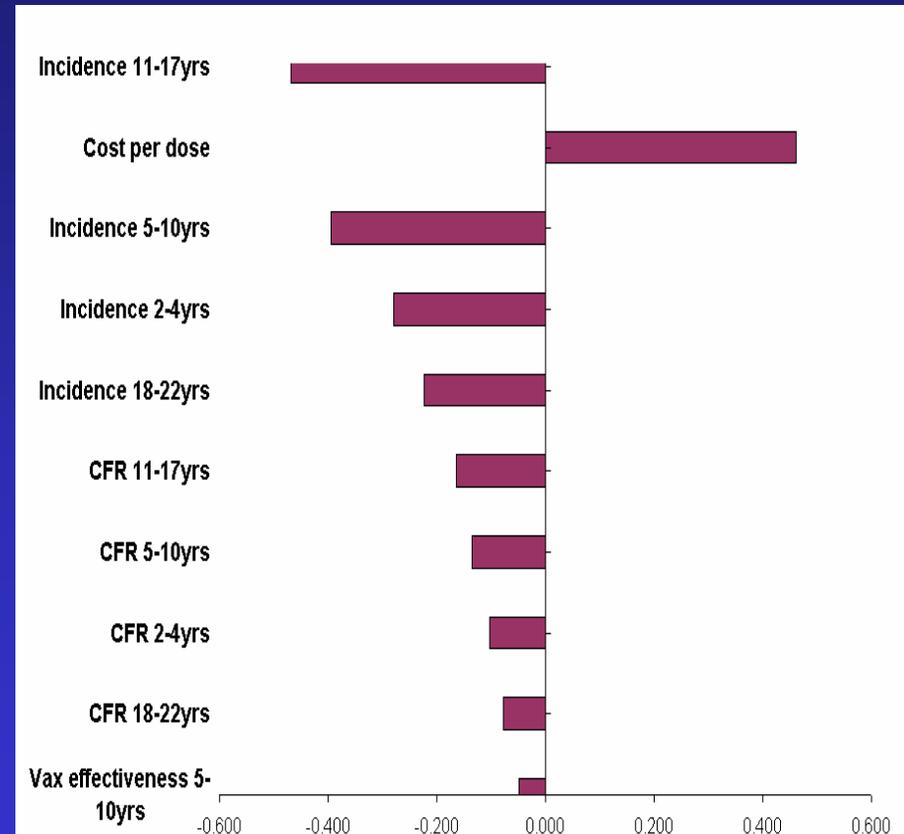
\$/Life-years saved “correlated” with inputs\*

**Toddlers 24mos**



Regression coefficient

**Toddlers 24mos + booster 11yr**



Regression coefficient

\* Estimates from Monte Carlo Simulation

# Working Group Considerations

Routine Vaccination

2-10 year-olds

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Burden of Disease

+/-

Population Impact

-

Economic Analysis

+/-

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Programmatic Implications

# MCV4 in 2-10 year-olds

- Comparative, modified double-blind study comparing to quadrivalent meningococcal polysaccharide vaccine (MPSV4)
  - All subjects received 4 doses of DTaP
  - N=696
  - Mean age 3.7 years (+-2.2), >80% 2-5 years
- Safety and immunogenicity

# Safety of MCV4 in 2-10 year olds

- No serious adverse events in either group
- Majority mild or moderate reactions
  - 91.4% of MCV4 recipients
  - 98.8% of MPSV4 recipients
- All reactions resolved without sequelae
- MCV4 recipients experienced more severe local reactions

# Proportion of study group presenting with reported solicited local reactions within 7 days of immunization

	MCV4	MPSV4
Local Reaction	N=692	N=700
Any local reaction	58.8%	58.3%
Redness	29.5%	30.4%
Swelling	20.5%	14.6%
Induration	22.1%	15.6%
Pain	48.1%	46.9%

# Working Group Considerations

Routine Vaccination

2-10 year-olds

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+/-

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+

Vaccine- Immune Response

Programmatic Implications

# Subjects with No Detectable Serum Bactericidal Antibody (<8) at Day 0 who Seroconverted (Titer $\geq$ 32) by Day 28

Serogroup	MCV4	MPSV4	P-value
A	98.6%	94.7%	0.005
C	87.9%	80.1%	0.002
Y	86.2%	75.0%	0.026
W-135	96.0%	89.6%	0.001

# MCV4: SBA GMTs, 2-10 year-olds: Serogroup C

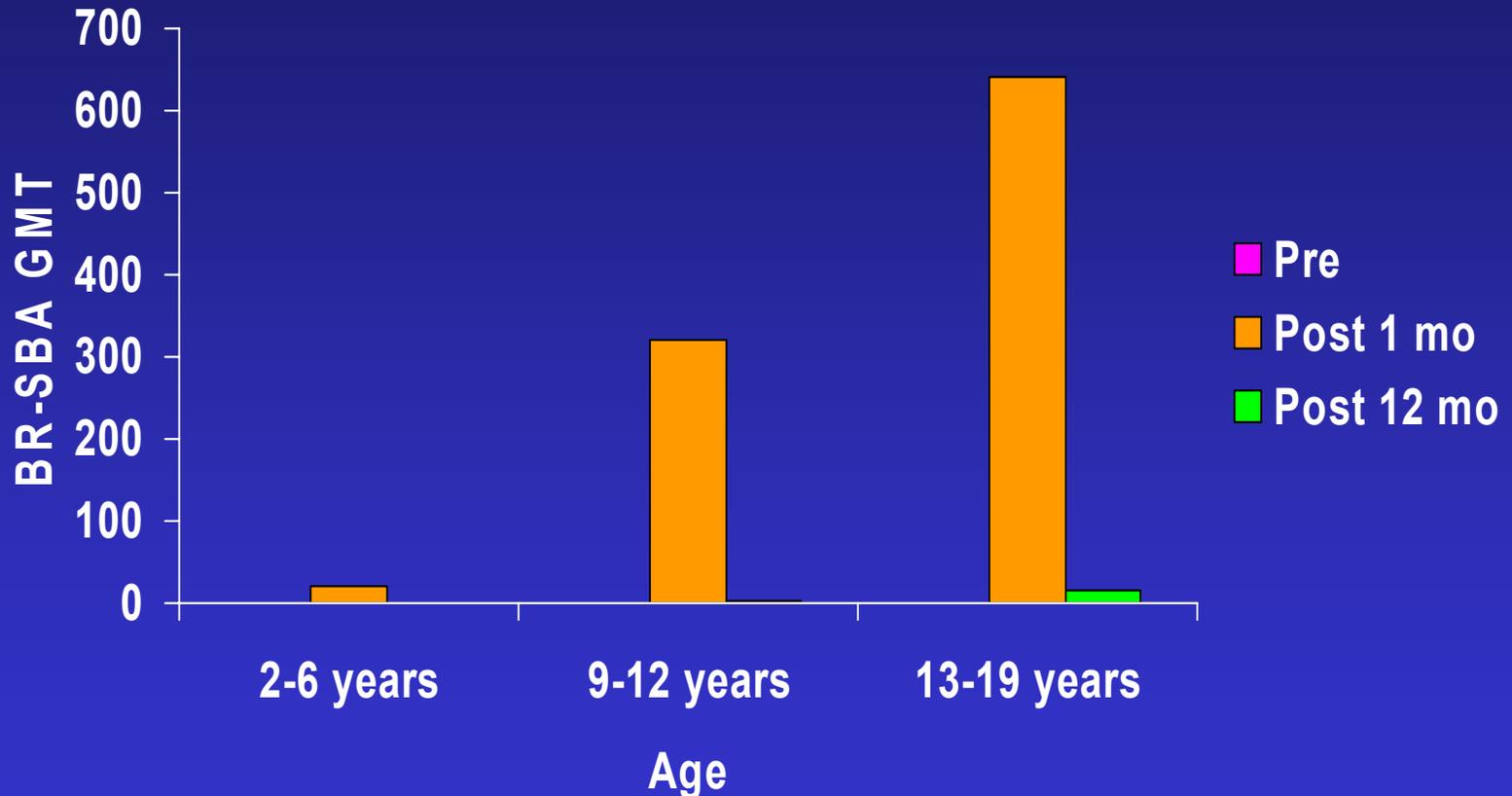
	MCV-4	MPSV-4*
Day 0	21 (18,24)	19 (16,22)
Day 28	354 (308,407)	231 (198,270)
6 months	137 (116,161)	66 (55, 79)

\*P<0.001

# Meningococcal Vaccines- Immune Response

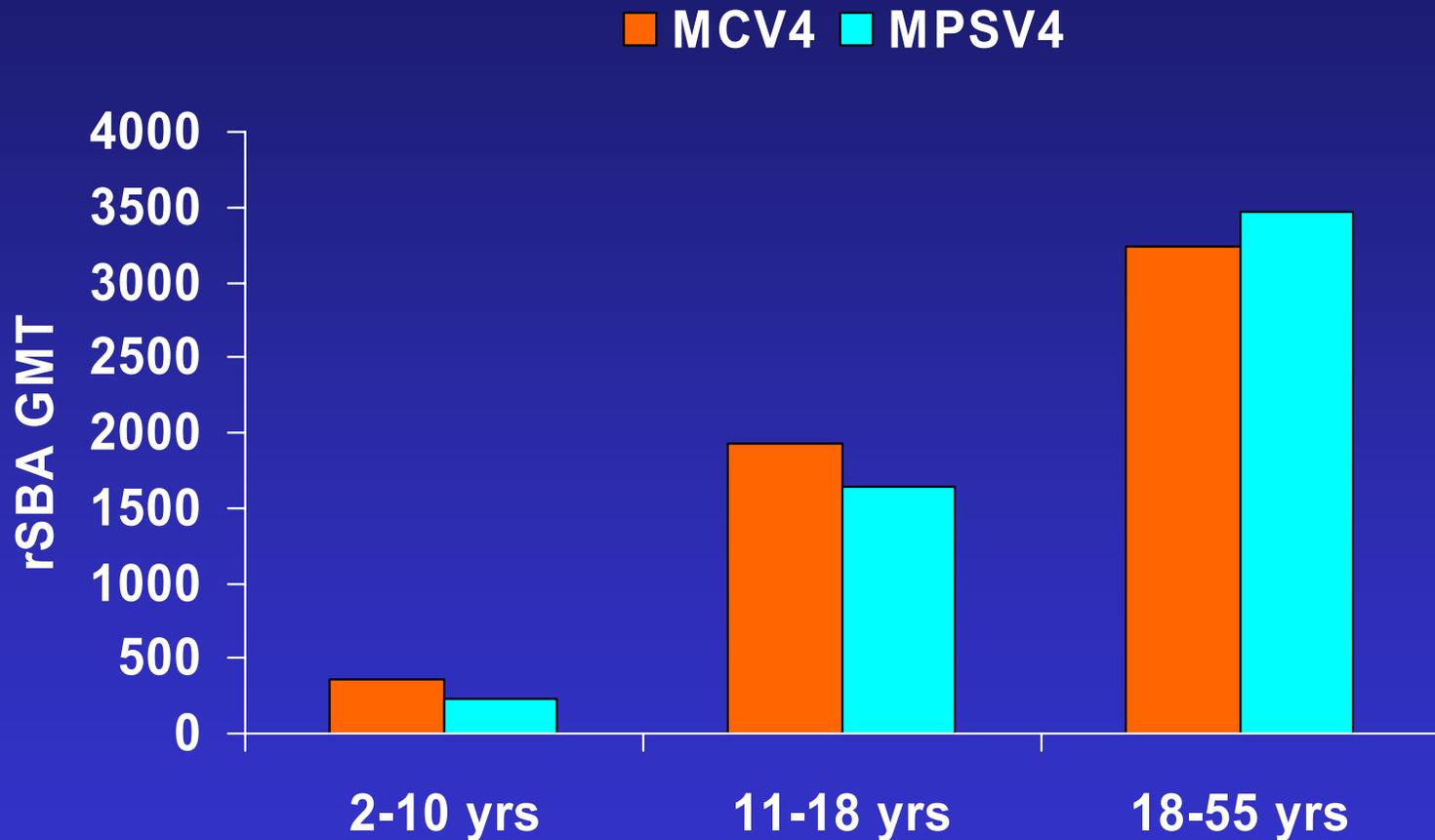
- MCV4 compared to MPSV4
- MPSV4 does *not* provide long-lasting protection in young children
- Conjugate vaccines should provide longer lasting protection than polysaccharide vaccines

# Age-Dependent Serogroup C SBA - MPSV4



Mitchell, L, Ochnio, J, and Glover, C. Analysis of Meningococcal Serogroup C-Specific Antibody Levels in British Columbian Children and Adolescents. *J Infect Dis* 1996;173:1009-1013.

# Serum Bactericidal Activity 28 days Post-MCV4: Serogroup C



Pichichero et al. *PIDJ*. 2005;24;57-62.

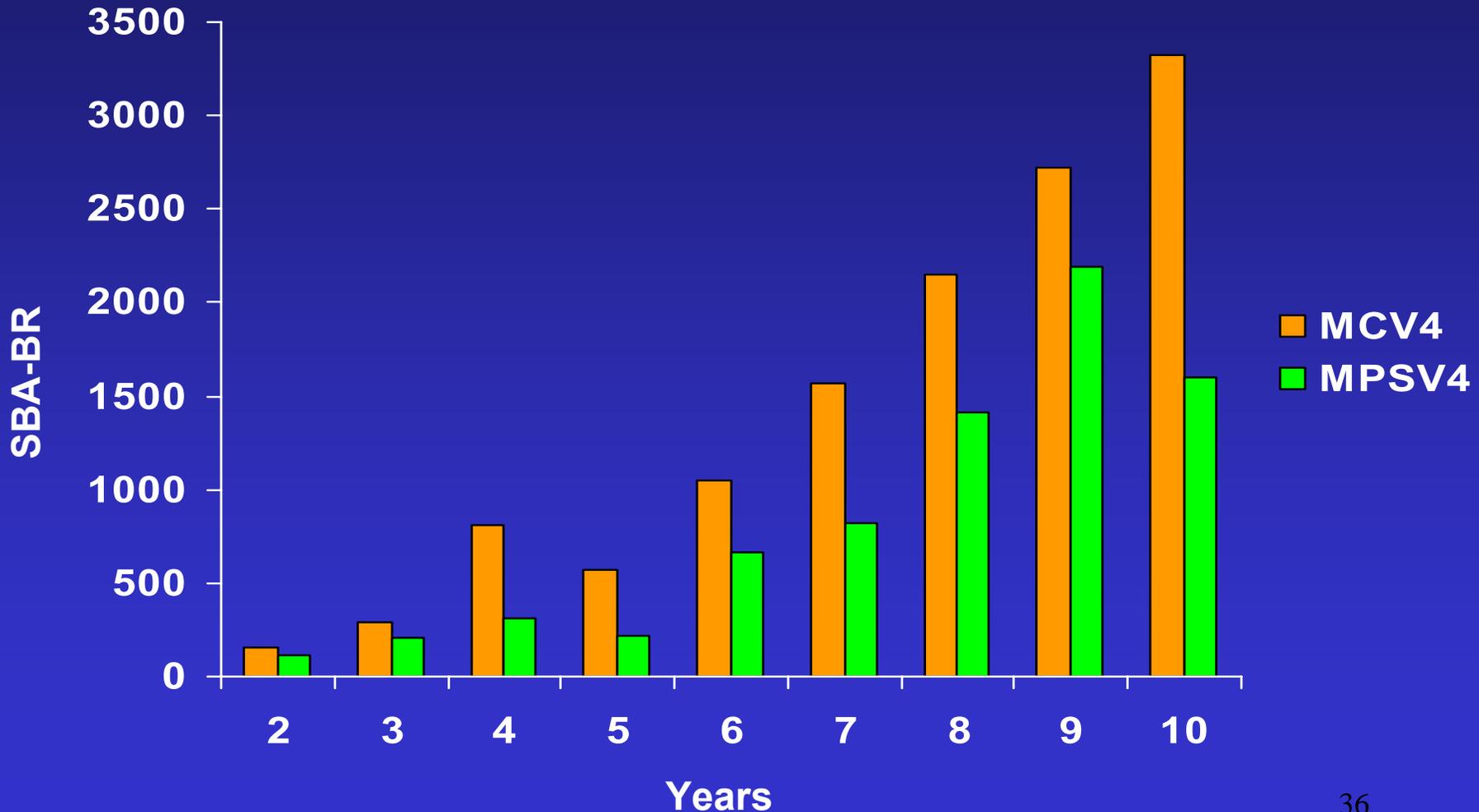
CDC. *MMWR*. 2005;54(RR 7)

# rSBA GMT 23-36 Months After Vaccination with MCV4 (2-3 years old)\*

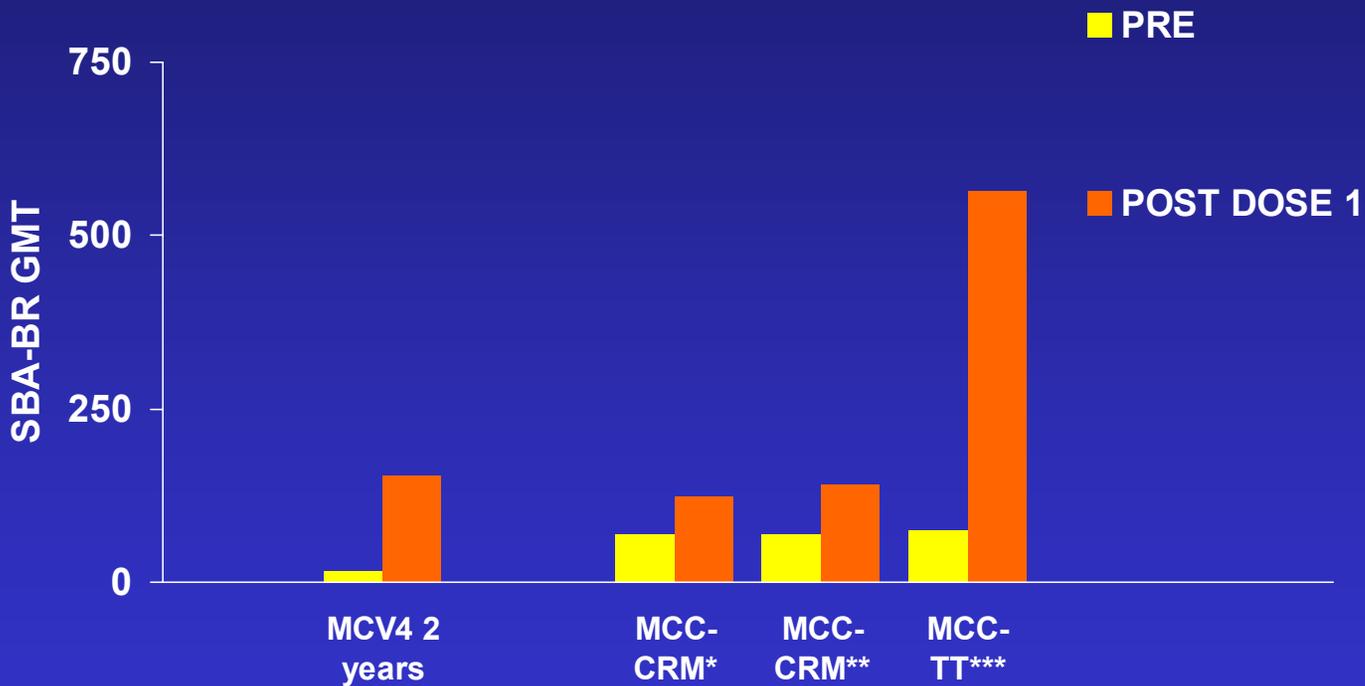
<b>Serogroup</b>	<b>MCV4-primed</b>	<b>MCV4-naive</b>
<b>A</b>	<b>256 (112,587)</b>	<b>141 (58,342)</b>
<b>C</b>	<b>59 (29,118)</b>	<b>17 (8,38)</b>
<b>Y</b>	<b>415 (265,649)</b>	<b>256 (120,547)</b>
<b>W-135</b>	<b>91 (45,181)</b>	<b>17 (9,33)</b>

\*Pichichero et al. PIDJ. 2006:25;995-1000.

# MCV4 vs. MPSV4 in Children 2–10 Years of Age (GMTs): Serogroup C



# Comparison of MCV4 at 2yrs vs Licensed MCC Vaccines (United Kingdom) in Toddlers, Serogroup C\*



Pichichero M., et. al. *PIDJ* 2005; 24:57-62

Richmond P., et. al. *JID* 2001; 183:160-3

\* Chiron \*\* Wyeth \*\*\* NAVA

\*Courtesy of Mike Decker,<sup>37</sup> Sanofi

# Working Group Considerations

Routine Vaccination

2-10 year-olds

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Burden of Disease

+/-

Population Impact

-

Economic Analysis

+/-

Vaccine Safety

+

Vaccine- Immune Response

+/-

Programmatic Implications

# Programmatic Considerations

- Currently no vaccine recommended at 2 year-old well-child visit
- Potential for meningococcal vaccines for infants/younger toddlers in near future

# Hepatitis A Vaccine at 2 years-old

- Recommended in 1999 to be routine in states with a high burden of hepatitis A (11 states)
- 1-dose coverage among 24-35 mo\*
  - 2004: 54.4% (range: 8.6%--74.4%)
  - 2005: 56.5% (range: 12.9%--71.0%)
- Routinely recommended for all children at 12 months in 2006 (licensure age lowered)

\*CDC. Hepatitis A Vaccination Coverage Among Children Aged 24-35 Months—United States, 2004-2005. 2007;56(27):678-681

# Protecting Young Children by Vaccinating During Infancy

## Immunogenicity of a Tetravalent Meningococcal Glycoconjugate Vaccine in Infants A Randomized Controlled Trial

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**Context** Immunization with a meningococcal tetravalent (serogroup ACWY) glycoconjugate vaccine is recommended for all US adolescents. However, the currently licensed vaccine is poorly immunogenic in infancy, when the highest rates of disease are observed.

**Objective** To determine the immunogenicity of a novel tetravalent CRM<sub>137</sub>-conjugated meningococcal vaccine (MenACWY) in infants.

**Design, Setting, and Participants** Randomized, open-label, controlled study of 225 UK and 196 Canadian 2-month-olds from August 2004 to September 2006.

**Intervention** UK infants received a primary course of MenACWY (at 2, 3, and 4 months or 2 and 4 months) or *Neisseria meningitidis* serogroup C monovalent meningococcal glycoconjugate vaccine (MenC) (at 2 and 4 months). All received MenACWY at 12 months. Canadian infants received MenACWY at 2, 4, and 6 months or 2 and 4 months; at 12 months they received MenACWY, a plain tetravalent polysaccharide vaccine, or no vaccine.

**Main Outcome Measure** Percentage of infants with a human complement serum bactericidal activity (hSBA) titer  $\geq 1:4$  after a primary course of MenACWY and after a 12-month booster. Safety and reactogenicity of MenACWY were also assessed.

**Results** According to the prespecified per-protocol analysis, the percentages (95% CIs) of MenACWY 2-, 3-, and 4-month recipients with hSBA titers  $\geq 1:4$  after primary im-

# Percent Responders (hSBA titers $\geq 1:4$ ) after primary 2,4,6 mo immunization with Men ACWY\*

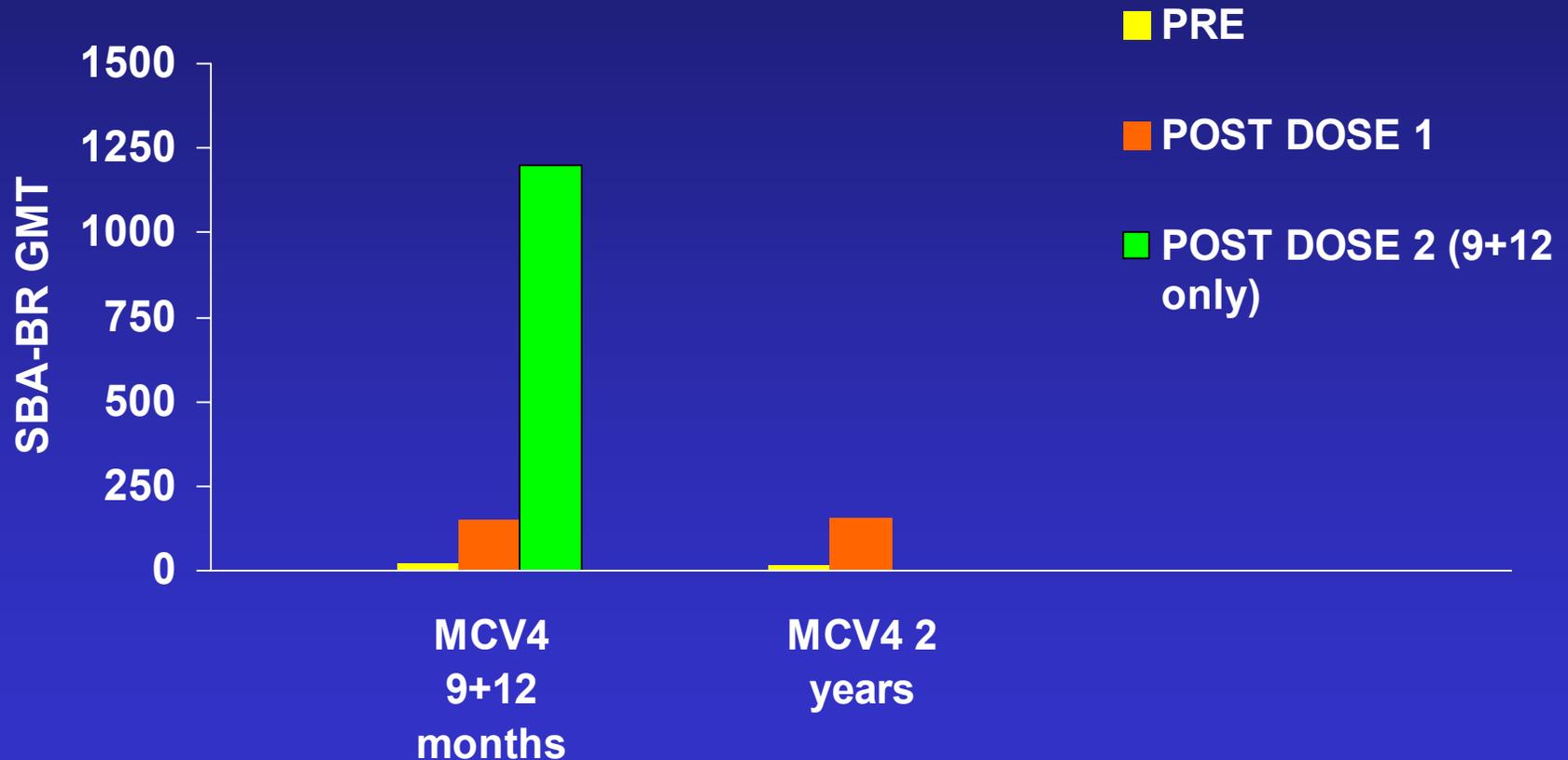
Serogroup	MenACWY at 2,4,6 months
A	81% (71-89%)
C	98% (92-100%)
Y	99% (93-100%)
W-135	98% (92-100%)

\*Snape et al. JAMA. 2008;299:173-184

# Percent Responders (hSBA titers $\geq 1:4$ ) after 9, 12 mo immunization with Menactra®

Serogroup	Menactra at 9, 12 months
A	97.2% (86-100)
C	100% (91-100)
Y	94.6% (82-99)
W-135	92% (78-98)

# Comparison of Menactra at 9+12 mos and 2 yrs, Serogroup C\*



Richmond P., et al. *JID* 2001; 183:160-3 Keyserling H., et al. Presented at the International Pathologic Neisseria Conference, Cairns Australia, 2007

# Working Group Considerations

Routine Vaccination

2-10 year-olds

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Burden of Disease

+/-

Population Impact

-

Economic Analysis

+/-

Vaccine Safety

+

Vaccine- Immune Response

+/-

Programmatic Implications

-

# Working Group Considerations

Routine Vaccination	2-10 year-olds	Adolescents
Burden of Disease	+/-	+
Population Impact	-	+
Economic Analysis	+/-	+/-
Vaccine Safety	+	+
Vaccine- Immune Response	+/-	+
Programmatic Implications	-	+

# Working Group Position

- Does not recommend routine vaccination against meningococcal disease in children aged 2-10 years at this time, except for children at increased risk of disease.
- If providers/parents choose to vaccinate against meningococcal disease in this age group, MCV4 is preferred to MPSV4.

# Acknowledgements

- ACIP Meningococcal Vaccine Working Group
- Kim Cushing
- Elizabeth Zell
- Paige Lewis
- Nancy Messonnier
- Thomas Clark